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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,341	01/04/2002	David Baltimore	75723-ZA/JPW/GJG	6591

23432 7590 06/26/2008

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EXAMINER	
GUZO, DAVID	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
06/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/037,341	BALTIMORE ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007 and 04 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90 and 91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90 and 91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 90-91 are rejected under 35 U.S.C. 102(b) as being anticipated by the Physician's Desk Reference (PDR: 1985) pages 1811-13; Griffith I (Griffith et al., Ann. Surg. 196 (9/82): 324-329) or Griffith II (Griffith et al., J. Thorac. Cardiovasc. Surg. 99 (12/84): 952-957) as evidenced by Holschermann et al., Circulation 96 (12/97) 4232-4238.

The rejection stands of reasons of record in the previous Office Action (Mailed 4/19/07) and for reasons outlined below. The rejection is expanded to include Claim 91 as a result of applicants' amendment filed 10/24/07.

Applicants have responded to the rejection by providing a 37 CFR 1.132 Declaration from Dr. Verma and providing arguments based upon assertions made in the Verma Declaration.

Declarant and applicants assert that the 1985 PDR reference provides no teaching that administration of cyclosporine (CsA) to patients serves to reduce **activated** NF-κB. Declarant and applicants assert that the 1985 PDR discloses administering the initial dose of cyclosporine 4-12 hours prior to transplantation and therefore the 1985 PDR cannot teach a method for reducing expression in a human cell

of a gene, the expression of which has been induced by an external influence that activates NF- κB, as recited by claim 90.

The Declaration under 37 CFR 1.132 filed 10/24/07 is insufficient to overcome the rejection of claims 90-91 based upon 35 USC 102(b) as set forth in the last Office action because of the following reasons.

Applicants' and declarant's arguments filed 10/24/07 have been fully considered but they are not persuasive. The 1985 PDR reference teaches administering the NF-κB inhibitor CsA to patients both prior to **and subsequent** to the transplant, thus rendering moot applicants' and declarant's argument that the reference does not teach prior activation (by the surgical procedure or by any of the normal ongoing biochemical influences activating NF-κB) in a human cell of a gene, the expression of which has been induced by an external influence that activates NF- κB.

With regard to the Griffith et al. I reference, applicants and declarant assert that Griffith et al. I provides no teaching that administration of cyclosporine (CsA) to patients serves to reduce **activated** NF-κB. Declarant and applicants assert that Griffith et al. I only teaches administration of CsA "orally just prior to operation" and hence is analogous to pretreatment and at best **prevents** activation of NF-κB by the surgery. Applicants and declarant also indicate that it is not clear if surgery induces NF-κB.

Applicants' and declarant's arguments have been considered but are not persuasive. Griffith et al. I clearly teaches administration of CsA **subsequent** to the transplant (see for example, the first paragraph of the Discussion section on p. 328) and hence applicants' and declarant's arguments, concerning administration of CsA only

prior to the operation in the Griffith et al. I reference, are unpersuasive. With regard to applicants' and declarant's indication that it is unclear if surgery induces activation of NF-κB, it is noted that applicants and declarant must be aware of the art teaching that inflammatory cytokine polypeptides (such as IL-1 and TNF, etc.) produced as a result of trauma (i.e. surgery) are well known to be activators of NF-κB (see for example Ebner et al. US 20070207943, whole document, particularly paragraph [0384]) and hence surgery would be expected to result in expression in a human cell of a gene, the expression of which has been induced by an external influence (surgery and concomitant production of IL-1, TNF, etc.) that activates NF- κB. Also, it is noted that within a human at any given time, cells are being influenced by external influences that activate NF-κB to act as an intracellular messenger to transmit a signal that induces expression of a given gene(s) in said cell and hence administration of CsA to a patient would be expected to inhibit transmission of the signal resulting from NF-κB activation and thereby reduce expression of the gene in said cell(s). Finally, with regard to the level of activation of NF-κB, the claims do not recite any level or degree of activation and hence any amount of activation of expression of a gene induced by NF-κB as a result of surgery would be sufficient to meet the limitations of the instant claims.

With regard to the Griffith et al. II reference, applicants' and declarant's arguments are essentially the same as presented traversing the Griffith et al. I reference, i.e. that Griffith et al. II does not teach prior activation in a human cell of a gene, the expression of which has been induced by an external influence that activates NF- κB.

In response, the examiner notes that Griffith et al. teaches post-operative administration of CsA to transplant patients and that surgery would be expected to result in expression in a human cell of a gene, the expression of which has been induced by an external influence (surgery and concomitant production of IL-1, TNF, etc.) that activates NF- κB. Applicants' and declarant's arguments are therefore not persuasive.

With regard to the Holschermann reference, applicants' and declarant assert that since the protocols differ greatly between the Holschermann et al. reference and the cited prior art references (1985 PDF, Griffith et al. I and II), Holschermann et al. cannot be used to explain what necessarily occurred in any of said prior art references. Applicants and declarant assert that different drug cocktails were used in Holschermann et al. vs the 1985 PDF and Griffith et al. references (as well as different administration protocols) and hence the results of the different treatments cannot be compared. Applicants and declarant assert that Holschermann et al. indicates that measurements of CsA in PBMCs and monocytes/'macrophages in blood samples revealed an increase in CsA in the samples before daily CsA administration and hence applicants assert that CsA was always present in the blood.

Applicants and declarant also assert that an examination of Figs. 3 and 4 of Holschermann et al. indicate that administration of CsA prevented the induction of TF mRNA by LPS as is indicated by the faint band in lane 7 and that CsA cannot reduce existing TF transcription, though it appears to prevent activation of TF. Furthermore applicants and declarant assert that an analysis of the data presented in Holschermann

et al. indicates that Holschermann et al. did not repeat the protocols followed in the other cited prior art references and that Holschermann et al. did not demonstrate that CsA reduced induced NF-κB activity.

In response, the examiner notes that it is **art recognized** that CsA does inherently affect NF-κB activity (i.e. abolishes inducible phosphorylation and degradation of IκB) consistent with the PDR 1985 and the Griffith et al. references as well as the Holschermann et al. disclosure. For example, Roman-Blas et al. (Osteoarthritis and Cartilage, 2006, Vol. 14, pp. 839-848) teaches therapeutic strategies based on the established role of immunosuppressive agents, including CsA, to inhibit the NF-KB pathway: "Cyclosporin A inhibits the protease activity of the 20S proteasome complex preventing I-κBα degradation in murine macrophages, Jurkat lymphoma cells, and mouse and human T- lymphocytes", p. 842 (right col. at bottom) to p. 843 (left col.) and also p. 843 under "Conclusion" to p.844 including Fig. 3.

As discussed above, the PDR 1985 and the Griffith I and II documents disclose (and enable) the use of cyclosporine (CsA) to treat cardiac transplant patients. Holschermann provides *ex vivo* and *in vitro* assay (TF-mRNA expression; EMSA determined NF-κB binding activity in lymphocytes and monocytes) evidence obtained from transplant patients (and controls) correlative to human utility to establish CsA's ability to inhibit NF-κB regulated gene (i.e. TF) expression. Holschermann further elucidates the *in vitro* and *in vivo* mechanism by which CsA inhibits NF-κB activation. Applicants and declarant have failed to provide any evidence to rebut the Holschermann teaching of the **inherent effect** of CsA upon administration to cardiac transplant

patients including those disclosed in the PDR 1985 and Griffith references. Nor have applicants and declarant provided evidence and/or a scientific rationale that the referred to method differences (including different drug cocktails) between Holschermann and the PDR 1985 and Griffith references would interfere with CsA's ability to regulate NF-KB-mediated gene expression.

With regard to applicants' and declarant's analysis of the data presented in Holschermann et al. and particularly in Figs, 3-4 and Table 2, it is noted that Holschermann et al. teach:

a. Fig: 1: In 10 samples from 10 different cardiac patients, isolated mononuclear cells had markedly increased TF generation after incubation with or without LPS compared with healthy control subjects (unrelated to increased monocyte counts).

b. Table 2: 10 samples of isolated mononuclear cells from 10 cardiac transplant patients before and after daily CsA administration were assayed for the effect of CsA on TF activity. Table 2 demonstrates that the degree of TF activity generated by mononuclear cells was inversely related to CsA blood levels and was reproducible. Additionally, both Fig. 2A and Table 2 show that monocyte TF induction was reduced after CsA application in all transplant recipients and "Likewise, a similar inverse relationship between CsA blood concentrations and TF inducibility was observed when highly purified monocytes/macrophages were analyzed instead of whole mononuclear cells (Fig. 2B)". Holschermann at page 4234 (with emphasis). Fig.1, 2 and Table 2.

Upon review of Fig. 2B it is clear that at least 9 out of 10 patient samples had decreasing TF activity with increasing CsA administration as indicated by negative

sloping lines. It's only with respect to the lowest amount of TF activity (about $10ml/10^6$ cells) that CsA administration had only a slight effect on decreasing TF activity that would be expected in light of the small TF sample amount capable of being induced.

The Holschermann Fig. 3 assay of TF-mRNA expression employs a dye (e.g. ethidium bromide) that is less sensitive than the radiolabel employed in Fig. 4 for detecting NF-κB in the EMSA assay and Fig. 3 is a colorimetric assay that is more difficult to visualize than the black and white radiolabel utilized in the Fig. 4 assay, especially when viewing a photocopy of a photocopy.

Upon viewing the original Holschermann document, even in black and white, the Examiner was able to visualize in Fig. 3 discernible bands representative of Lane 2 (*ex vivo* unpurified) and particularly Lane 3 (more pure sample), both of which represent the presence of TF mRNA in the ex-vivo blood samples. This observation is consistent with the Holschermann teaching (p.4235, right column, with emphasis) that

> "Cells obtained from transplant recipients in the presence of low baseline CsA blood levels (sample before CsA administration) exhibited moderate TF mRNA expression in the absence of LPS" (representative of Fig. 3 Lanes 2 and 3) and "a strong TF mRNA expression when challenged with LPS" (representative of Fig. 3, Lane 4 which is more readily visible).

Thus, contrary to patentee's argument, the presence of NF-κB in human transplant patient's PBM's shown in the EMSA assay Fig. 4 Lanes 1-3 **correlates with** moderate TF mRNA expression in the same transplant patient as indicated in the Fig. 3 assay.

Applicants and declarant assert the cited references do not provide enough detail to enable the skilled artisan to repeat their studies and arrive at the same results.

Applicants and declarant assert that the lack of availability of the patient populations used in prior studies and the inherent variability in patients' responses to CsA would not enable one of skill in the art to practice the 1985 PDR and Griffith et al. studies and obtain the same results.

In response, the examiner notes that Holschermann (p. 4232, right column under "Methods" to p. 4233) describes the demographics of the ten heart transplant recipients and their "Baseline Patient Characteristics" (see Table 1) from which blood was extracted and purified for use in their assays and further discusses in detail the electrophoretic mobility shift assay (EMSA) utilized (see pp.4233-4234) to obtain the Fig. 4 data.

Regarding reproducibility, the article further indicates (p.4236, left column; and Fig. 4) that "In cells obtained from transplant recipients during low baseline CsA blood levels (before CsA administration), strong NF-κB binding activity was detected" and that the "[S]pecificity of the binding reaction ,was shown by the competition with unlabeled consensus oligonucleotides" in which the "[A]nalysis was performed in triplicate". See explanation under Fig. 4 page 4236.

Enablement, and not actual reduction, is required for anticipation. As discussed above, the Holschermann document (p 4232, right column under "Methods" to p.4233). describes in detail the demographics of the ten heart transplant recipients and their "Baseline Patient Characteristics:' (see Table 1) from which blood was extracted and purified for use in their assays and additionally discusses in detail the EMSA assay utilized (see pp. 4233-4234). Further, patient variability, toxicity and side effects are

common variables in any clinical study and the demographics and patient number in the Holschermann study would be expected to adequately account for these variables.

Regarding Holschermann's statement of observing a high inter-individual variation in monocyte TF inducibility, Holschermann goes on to further indicate that their study nevertheless showed that the levels of monocyte TF expression remained essentially constant in individual patients. See Holschermann p.4237, right column first full paragraph.

Accordingly, Holschermann provides a sufficient basis from which one could infer that the patients studied were characteristic of transplant patients treated with CsA as described in the 1985 PDR and Griffith et al. studies.

With regard to new claim 91, the extracellular polypeptide that activates NF-κB can be the inflammation induced cytokines IL-1 and TNF which activate NF-κB and would be produced as a consequence of the trauma resulting from the surgery recited in the cited references. Also, as cytokines such as IL-1 and TNF, etc. are normally produced in the human body as a result of normal inflammation reactions, it must be considered that said polypeptide activators of NF-κB would be present to activate NF-κB prior to the administration of CsA as recited by the cited references. The cited references therefore anticipate Claim 91.

Obviousness Type Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 90-91 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 9-17, 20-63, 88-176 and 192-203 of U.S. Patent No. 6,410,516. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons of record in the previous Office Action and for reasons outlined below. Newly added claim 91 is obvious in that claims in the '516 patent (see in particular claim 9) recite methods for reducing expression in human cell of a gene which has been induced by an extracellular influence that activates NF-κB. The specification of the '516 patent specifically discloses extracellular polypeptides as embodiments of the extracellular influences which activate NF-κB and hence said embodiment would have been obvious to the ordinary skilled artisan.

Applicants have responded to this rejection by indicating that they will file a Terminal Disclaimer upon indication of allowable subject matter should the allowable subject matter so require.

The rejection will therefore be maintained.

Claims 90-91 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 89 of copending Application No. 10/037,415. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons of record in the previous Office Action and for reasons outlined below.

Instant claim 90 recites the same method as recited in the ‘415 application but is broader in reciting any external influence rather than an extracellular polypeptide. The ‘415 claim would anticipate the instant claim 90. With regard to instant claim 91, both the instant claim and claim 89 of the '415 application recite reducing expression of a gene which has been induced by an extracellular polypeptide that activates NF-κB. The claims differ in that the ‘415 claim is narrower in scope in reciting a signal that induces expression of the gene from the plasma membrane of the cell to the nucleus of the cell while the instant claim 91 broadly recites any signal that induces expression of the gene. The instant claim 91 would therefore anticipate claim 89 of the '415 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have not traversed this rejection and therefore the rejection stands.

Any rejection not repeated in this Office Action is withdrawn

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 16, 2008

/David Guzo/
Primary Examiner
Art Unit 1636